REMARKS

Claims 1 - 42 are now pending in the application. Claims 1, 41 and 42 are currently amended, claims 20, 21 and 38-40 were previously amended, claims 2 - 19 and 22-37 are original. A copy of the claims now pending in the application showing changes made to currently amended claims in accord with 37 CFR 1.121, as revised, has been provided. No new matter has been introduced by virtue of the amendments made herein. Accordingly, applicants respectfully request their entry. In view of the amendments made herein and the remarks below, applicants respectfully request reconsideration and withdrawal of the rejection set forth in the November 5, 2003 office action.

Rejection under 35 USC § 103(a)

The Examiner acknowledged receipt of Amendment B dated August 18, 2003 but declared the arguments therein moot in view of the new grounds of rejection. The Examiner rejected claims 1-5, 6-10 and 15-42 under 35 USC § 103(a) as being unpatentable over WO 00/06161 to Jackson et al, in view of US Patent 5,112,621 to Stevens et al.

Without prejudice to applicants' rights and in the interests of facilitating prosecution the applicants have amended claims 1, 40 and 41. Claim 1 now defines the coating layer as "consisting of", rather than "including", one or more acrylic copolymers and as optionally including "one or more of a plasticiser, an anti-tacking agent or a wetting agent". Support for this amendment is found in the paragraph spanning pages 6 and 7 of the instant application where it is stated that "The water insoluble, permeable coating may include one or more additional substances other than an acrylic copolymer containing trimethylammoniumethytmethacrylate groups". This sentence clearly implies, by the use of the word "may" that in one embodiment the coating consists entirely of acrylic copolymers. The paragraph continues to explain that if the coating comprises a substance other than an acrylic copolymer then such a substance may be a plasticiser (page 6, line 33), an anti-tacking agent (page 7, line 5) or a wetting agent (page 7, line 7).

Process claims 41 and 42 have been amended in accordance with the amendment to claim 1. In addition, in order to more completely claim the invention, claim 41 refers to claim 2 as well as claim 1 and claim 42 refers to claim 3 as well as claim 1.

WO-A-00/06161 (page 7, line 29) proposes that eletriptan, or a salt thereof, can be administered in the form of a sigmoidal releasing pellet by applying the technology disclosed in US-5,112,621 in relation to diltiazem. US Patent 5,112,621 discloses a coating mixture comprising ethyl cellulose and an acrylic resin. The applicants submit that it should be noted that the reference in WO-A-00/06161 to "sigmoidal releasing pellets (e.g. as referred to in US Patent no. 5,112,621)" clearly refers to the new invention disclosed in US-5,112,621 ("The present

invention provides a sustained-release pharmaceutical composition which comprises microparticles comprising an active principle, said microparticles being coated with a coating mixture comprising ethyl cellulose and an acrylic resin...") and not to a particle coated solely with Eudragit RS which is mentioned in US-5,112,621 solely for comparative purposes.

The applicants have conducted experiments to assess whether the teaching of WO-A-00/06161 is correct in respect of its proposal that a sigmoidal release composition of eletriptan could be prepared by substituting eletriptan for diltiazem in the composition disclosed by US-5,112,621. The results of these experiments are summarized in Annex 1. The results demonstrate that when the coating disclosed in US-5,112,621 is applied to drug cores containing eletriptan hemisulphate, rather than diltiazem, a sigmoidal pattern of drug release is not obtained.

Instant claim 1 relates to a pharmaceutical composition comprising eletriptan, or a salt thereof, which is capable of achieving a sigmoidal pattern of controlled drug release by use of a water insoluble, permeable coating consisting of one or more acrylic copolymer(s) containing trimethylammoniumethylmethacrylate groups and, optionally, one or more of a plasticiser, an anti-tacking agent or a wetting agent.

None of the cited prior art discloses such a pharmaceutical composition. In particular, the coating disclosed in US-5,112,621 additionally comprises ethyl cellulose.
None of the cited prior art documents discloses a formulation of eletriptan, or a salt thereof, which is capable of delivering a sigmoidal pattern of controlled drug release. The objective problem solved by the present application in light of any of the cited prior art is thus the provision of a formulation of eletriptan, or a salt thereof, capable of delivering such a pattern of sigmoidal drug release. The problem is solved by the invention as presently claimed, as demonstrated by Example 6 in the application.

None of the cited prior art suggests that a controlled release coating consisting of acrylic copolymers alone (or in conjunction with one or more standard pharmaceutical excipients selected from a plasticiser, an anti-tacking agent and a wetting agent) would solve the objective problem outlined above. In particular, ethyl cellulose is an essential feature of the disclosure of US-5,112,621 and there is no suggestion that it may be dispensed with. US-5,112,621 therefore teaches away from instant claim 1. The applicants submit claim 1, as currently amended, is patentable under 35 USC § 103(a) over the cited references, either separately or in the combination cited by the Examiner, and respectfully requests withdrawal of the rejection. The applicants further submit that currently pending claims 2-10 and 15-42 all of which incorporate the novel and unobvious features of claim 1, are all patentable under 35 USC § 103(a) over the cited references, either separately or in the combination cited by the Examiner, and respectfully request withdrawal of the rejection.

In view of the above arguments the applicants further request withdrawal of the objection to claims 5 and 11-14 which the Examiner deemed allowable if not dependent on a rejected base claim.

In view of the amendments set forth herein and remarks above, the applicant respectfully submits that the pending claims are fully allowable, and solicits the issuance of a notice to such effect. If a telephone interview is deemed to be helpful to expedite the prosecution of the subject application, the Examiner is invited to contact applicant's undersigned attorney at the telephone number provided.

The Commissioner is hereby authorized to charge any fees required under 37 C.F.R. §§1.16 and 1.17 or to credit any overpayment to Deposit Account No. 16-1445.

Date: March 16, 2004

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Annex 1 - Experiment to assess whether the combined teaching of D1 and D2 provides a sigmoidal controlled release formulation of eletriptan

1. Materials used

The following materials were used in the experiments described below:

Ingredient	Function	Supplier
Eletriptan hemisulfate	Drug	Pfizer
Sugar spheres 600-710 μm	Cores	Pfizer
Hydroxypropylmethylcellulose Methocel E3	Binder	Colorcon
Talc Pharm S USP	Antisticking agent	Lucenac
Ethylcellose Ethocel N 22 NF	Release rate modifier	Hercules
Eudragit RS	Release rate modifier	Röhm
Acetylated monoglyceride Myvacet 9-45	Plasticizer	Quest
Na carboxymethylcellulose Cekol 30	Binder	Noviant

2. Preparation of beads

A. Attempted extrusion/spheronization

An attempt was made to manufacture drug-containing microparticles using extrusion/spheronisation, as recommended by US-5,112,621 (column 2, line 42). The following ingredients were used:

Ingredient	Type	Amount, g	Amount, %
Eletriptan hemisulphate	Drug	120	80
Microcrystalline cellulose	Avicel PH 101	30	20
Na carboxymethylcellulose*	Cekol 30	q.s.	q.s.

* used as 5 % w/v aqueous solution (granulation fluid)

However, using eletriptan hemisulphate rather than diltiazem, it was not possible to prepare pellets by extrusion/spheronization. Therefore, drug cores were manufactured by layering onto sugar spheres.

B. Drug layering on sugar spheres

Methocel E 3 (30.3g) was dispersed in warm purified water (1299.9g, 60°C) using a magnetic stirrer until no lumps were visible. The mixture was cooled to room temperature (using ice water) with stirring until a clear solution was obtained. Eletriptan hemisulfate (403.0g) was added to the solution and stirring was continued until a clear solution was obtained. Talc (86.7g) was added and dispersed in the solution by stirring until no lumps are visible.

Sugar spheres (400g) were layered with the above solution under the following conditions:

Equipment	**Aeromatic STREA 1**
Inlet air temperature, °C	68
Outlet air temperature, °C	40
Airflow, m³/h	110
Nozzle diameter, mm	1.2
Spraying pressure, bar	2
Spray rate, g/min	8.6-11.9
Drying at 40°C, min	15 min

Coating solutions for the coated sugar cores were prepared using the following ingredients:

Ingredient	**Weight, g**	
	Batch # El. 2.1	**El. 2.2**
Ethylcellulose N 22 NF	19.68	19.68
Eudragit RS	30.30	24.00
Acetilated monoglycerides Myvacet 9-45	4.32	4.32
Isopropanol	676.84	676.84
Dem. Water	75.21	75.21

Eudragit RS, ethylcellulose and Myvacet 9-45 were dispersed in a mixture of isopropanol (676.84g) and water (75.21g) using a magnetic stirrer. The mixture was stirred overnight (> 16 h) until complete dissolution was obtained.

The eletriptan hemisulphate cores were coated under the following conditions at levels of 4, 6 and 8%:

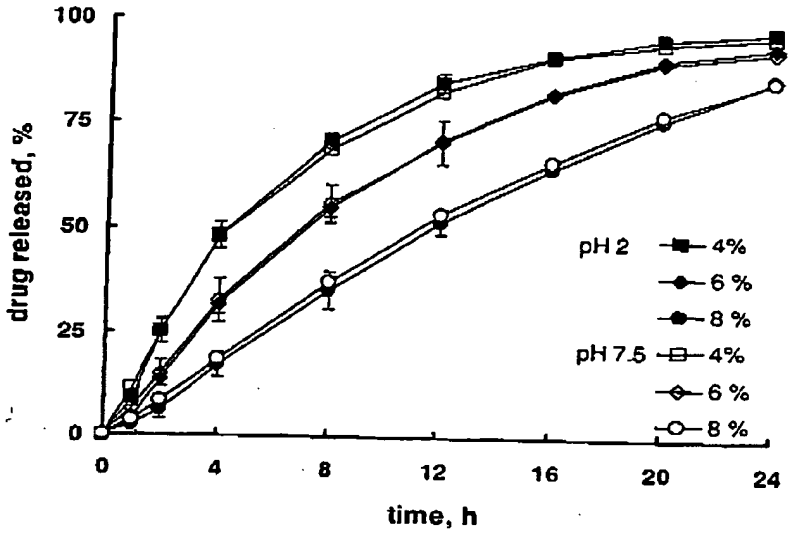
Equipment	**Uniglatt lab coater**
Eletriptan layered pellets, g	400
Inlet air temperature, °C	36
Outlet air temperature, °C	30
Airflow, m³/h	30
Nozzle diameter, mm	1.2
Spraying pressure, bar	2
Spray rate, g/min	2.9-6.8
Drying at 40°C, min	15

3. Drug release from beads

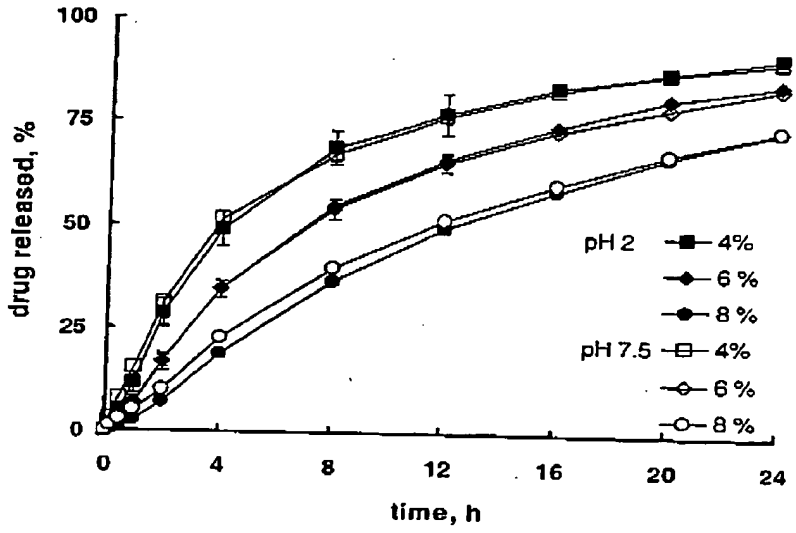
The drug release characteristics of the two batches of coated beads El. 2.1 and El. 2.2 was assessed in a USP XXIV basket apparatus (Vankel 300) at 100 rpm, 37°C at pH 7.5 (900 ml of pH 7 buffer solution) and at pH 2 (0.01 N hydrochloric acid, containing 5.23 g/l NaCl).

The following patterns of drug release were obtained:

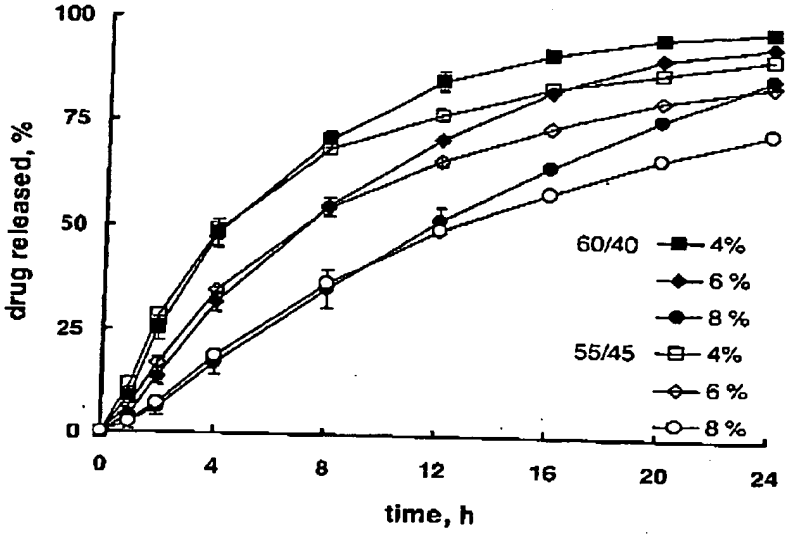
El. 2.1 Eletriptan Pellets, Uniglatt
Eudragit RS/EC N 22 60:40, pH 2/pH7.5
coating level (n=3)



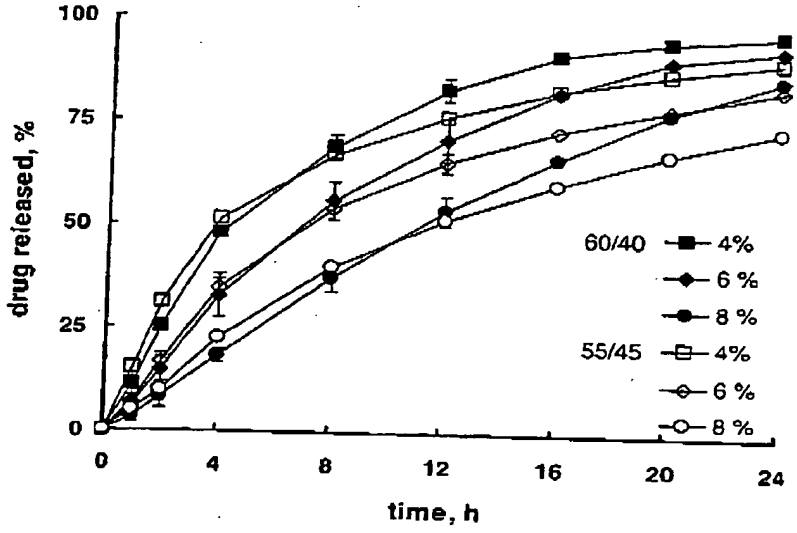
El. 2.2. Eletriptan Pellets, Uniglatt
Eudragit RS/EC N 22 55:45, pH 2/pH 7.5
coating level (n=3)



El. 2.1/El. 2.2 Eletriptan Pellets, Uniglatt
pH 2
Eudragit RS/EC N 22 ratio, coating level (n=3)



El. 2.1/El. 2.2 Eletriptan Pellets, Uniglatt
pH 7.5
Eudragit RS/EC N 22 ratio, coating level (n=3)



4. Conclusions

(a) The pattern of drug release from the coated pellets was independent of pH.
(b) The drug release of pellets coated with an Eudragit RS/EC ratio of 55/45 was slightly slower than the release of beads coated with a ratio of 60/40.
(c) **The pattern of drug release was not sigmoidal.**